UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,504	05/12/2006	Hiroyuki Tsunoda	14875-153US C1-A0320Y2P-U	8020

26161 7590 04/15/2009

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
04/15/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,504	TSUNODA ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 32-43* is/are pending in the application.

4a) Of the above claim(s) *9,10,19-22,29 and 34-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-18,23-28,32,33,38,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/23/07,10/4/07,2/12/08,6/11/08,8/29/08,9/29/08,11/20/09,2/24/09,3/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicants' amendment of 23 December 2008 is acknowledged and made of record. Claims 16-18, 23-25, and 28 have been amended. Claims 30 and 31 are canceled.

Restriction Requirement:

In the response of 29 September 2008 to the Restriction Requirement of 27 June 2008, Applicants elected, with traverse, Group IV, claim 32, drawn to an antibody that "recognizes the region of amino acids 26-274 of human MPL". In Office Action of 12 December 2008, the Examiner rejoined claims 1-8, 11-15, 33, 42 and 43. Claim 38 was also rejoined. The Examiner also required Applicants to elect a single ultimate species, including all included CDR's and Framework regions, and to further disclose which CDRs and framework regions correspond to the ultimate species.

In response of 23 December 2008, Applicants elected the antibody recited in claim 28(a). The heavy chain variable region of the elected antibody comprises the amino acid sequence of SEQ ID NO:229 and the light chain variable region of the elected antibody comprises the amino acid sequence of SEQ ID NO:238. The heavy chain variable region specified by SEQ ID NO:229 includes CDR1, CDR2 and CDR3 identified by SEQ ID NOs:36, 37 and 38, respectively and FR1, FR2, FR3 and FR4 identified by SEQ ID NOs:230, 232, 234, and 236, respectively. The light chain variable region specified by SEQ ID NO:238 includes CDR1, CDR2 and CDR3 identified by SEQ ID NOs:93, 94 and 95, respectively and FR1, FR2, FR3 and FR4 identified by SEQ ID NOs:239, 241, 243 and 245, respectively.

In response of 23 December 2008, Applicants request that Examiner rejoin claims 39-41 because these claims properly depend from claim 32.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons

Identification of an antibody which recognizes an epitope within the region of amino acids 189-245 of human Mpl or an antibody which recognizes an epitope within the region of amino acids 213-231 of human Mpl would require additional searches of the databases. A search for an antibody that recognizes the region of amino acids 26-274 of human Mpl would not identify art which anticipates or renders obvious an antibody that recognizes a smaller, specific fragment of human Mpl.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 1-29, and 32-43 are pending in the instant application. Claims 9, 10, 19-22, 29, and 34-41 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-8, 11-18, 23-28, 32, 33, 38, 42 and 43 are under consideration to the extent they read on the elected invention.

Priority:

Acknowledgment is made of applicant's claim for foreign priority based on the following applications filed in Japan:

Japan 2003-415746, filed 12/12/2003

Japan 2004-071763, filed on 3/12/2004

Japan 2004-248323, filed on 8/27/2004.

It is noted, however, that applicants have not filed certified English translations of any of the documents. Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

For purposes of prior art, priority is granted to the date of filing of PCT/JP04/18506., 10 December 2004

Information Disclosure Statement:

The Information Disclosure statements (IDSs) submitted on the 4 October 2007, 12 February 2008, 11 June 2008, 29 August 2008, 29 September 2008, 20 January 2009, 24 February 2009, and 5 March 2009 has been considered. The signed copies are attached.

The information disclosure statement filed 23 May 2007 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because references A16-A21 are not in English and no English abstract has been provided, nor have the relevant portions been identified. These references have been lined through and not considered. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

It is noted that applicants have referenced patent and nonpatent literature in the specification [paragraph 0008 of PGPUB 20060222643, the PGPUB of the instant invention]. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Abstract:

The abstract of the disclosure is objected to because it is written in two paragraphs. Correction is required so that the abstract reads as a single paragraph. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single

paragraph on a separate sheet within the range of 50 to 150 words. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claims:

Claim 1 is objected for reciting the short form of the receptor as "TPO". The receptor should be identified in full the first time it is recited in the claims. It is suggested the claim be amended to recite “thrombopoietin (TPO) receptor”.

Claim 42 is objected to because of the following informalities: a transitional phrase is omitted in line 8 of the claim; “light chain variable region SEQ ID NO:…” should be amended to read “light chain variable region *comprises* SEQ ID NO…”.

Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 16-18, 23-28, 32, 33, 38, 42 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to an antibody “having binding activity against TPO receptor (mpl)”. It is unclear what applicants intend by the phrase “binding activity against…”. It is unclear if the antibody is to bind to the TPO receptor or to act as an antagonist of the TPO receptor, that is, inhibiting activation of the receptor, or something else entirely.

Claim 32 is vague and indefinite in reciting “region of amino acids 26 to 274 of human Mpl" without specifically identifying the sequence of human Mpl. The disclosure teaches human Mpl molecules are known to exist in two forms comprising 572 and 635 amino acids [paragraph 0002]. Additionally, "Mpl of the present invention may be a mutant receptor" [paragraph 0139]. Therefore, without identification of the sequence of human Mpl, the metes and bounds of the claim cannot be determined.

The remainder of the claims is included as depending from a rejected claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1-3, 11-15, 32, 33 and 38 are directed to antibodies of unidentified CDR regions which bind to TPO receptor. Claims 42 and 43 are drawn to an antibody

comprising a heavy chain variable region containing a CDR1, CDR2, and CDR3 of SEQ ID NOs: 36-38 respectively in which one or more amino acids have been substituted, deleted, added and/or inserted, said antibody having the same activity as a second antibody whose heavy chain variable region comprises SEQ ID NOs: 36-38 and whose light chain variable region SEQ ID NOs 93-95. Given the broadest reasonable interpretation, the claims are drawn to an antibody comprising a heavy chain variable region in which the three CDRs can contain any unspecified sequence or an unspecified number, of substitutions, deletions, additions and/or insertions in the amino acid sequence of said CDRs. Since the upper limit of substitutions, deletions, additions and/or insertions has not been specified, the entire CDR1, 2 and/or 3 domain may be substituted; thus the antibody may comprise a heavy chain variable region comprising CDRs of any, unidentified amino acid sequences as long as the ability to recognize the region of amino acids 26-274 of human Mpl is retained.

The scope of the patent protection sought by Applicants as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons.

The specification teaches antibodies that bind to the TPO receptor (Mpl) [paragraph 0137] preferably have agonistic activity to Mpl [paragraph 0141]. The disclosure identifies humanized antibodies comprising heavy chain variable regions and light chain variable regions of specified sequences [paragraph 0165] and identifies specific CDRs and FRs (framework regions) which are included in the heavy and light chain variable regions [paragraphs 0168-0188, and 201-204]. While the specification discloses antibodies comprising heavy and light chain variable sequence comprising CDRs in which one or more amino acids have been substituted, deleted, added, and/or inserted, wherein the antibody retains the ability to bind to the TPO receptor [paragraph 0205], insufficient guidance is presented as to which amino acids in the CDRs of the heavy chain variable regions must be retained in order that the required activity of the antibody be preserved. The working examples (See example 2 and 3) are all drawn to constructing and utilizing antibodies comprising heavy and light chain variable regions of consisting of specifically identified CDRs. There are no examples of construction or

utilization of CDRs in which one or more amino acids have been substituted, deleted, added, and/or inserted.

General guidance is presented in the disclosure regarding how to make and test variants of the disclosed antibodies [paragraphs 0205, 0206, and 0263-0267]. However, the problem of predicting antibody structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the antibody is extremely complex. While it is known that many amino acid substitutions are generally possible in any given antibody within the antibody's sequence (for example, the framework region), where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the antibody's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 433-506). However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the antibody which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active antibody variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Due to the large quantity of experimentation necessary to generate the infinite number of variant antibodies recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to retain antigen-binding activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes

the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Written Description

Claims 1-3, 11-15, 32, 33, 38, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

The claims are drawn to antibodies of unidentified CDR regions which bind to TPO receptor or antibodies comprising a heavy chain variable region containing a CDR1 amino acid sequence of SEQ ID NO:36 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, a CDR2 amino acid sequence of SEQ ID NO:37 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, and a CDR3 amino acid sequence of SEQ ID NO:38 in which one or more amino acid residues has been substituted, deleted, added and/or inserted. The claims do not require that any particular portion of the amino acid sequence of the CDR be conserved; substitution of all the amino acid residues of all three CDR regions would meet the limitations of the claims. Thus, the claims are drawn to a genus of antibodies that are defined only a required function, that of recognizing an unspecified epitope within the region of amino acids 26-274 of human Mpl. There is no structural requirements recited which correlate with the required recited function of the antibody encompassed by the claims.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of

making the claimed product or any combination thereof. In this case, the only factor present in the claim is a required function, that of recognizing an unspecified epitope within the region of amino acids 26-274 of human Mpl. There is not even identification of any particular portion of the amino acid sequence of any of the CDRs that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of antibodies and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is antibodies comprising a heavy chain variable region containing a CDR1 amino acid sequence of SEQ ID NO:36 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, a CDR2 amino acid sequence of SEQ ID NO:37 in which one or more amino acid residues has been substituted, deleted, added

and/or inserted, and a CDR3 amino acid sequence of SEQ ID NO:38 in which one or more amino acid residues has been substituted, deleted, added and/or inserted. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

35 U.S.C. § 102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

For purposes of prior art, priority is granted to the date of filing of PCT/JP04/18506., **10 December 2004**.

Claims 1, 5-8, 11-15, 32, 33, 38, 42, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al (2002. US 6,342,220, the '220 patent, cited on IDS of 23 May 2007, reference A5)

The '220 patent teaches antibodies or fragments thereof that activate the TPO receptor. This agonist antibody activates a human c-mpl (column 9 line 59 bridging

column 10, line 1). The reference teaches fragment agonist antibodies including Fv, ScFv, Fab, $F(ab')_2$, diabodies and linear antibodies (column 10, lines 2-5) including single chain antibodies (Claim 10). These antibody fragments are encompassed by the term "minibody" as recited in the claims of the instant invention [paragraph 0142 of the instant specification]. Thus, the limitations of claim 1, 7, 32 and 33 are anticipated. The antibody fragments may be linked to other sequences, including the Fc region of an antibody, thereby forming a chimeric antibody (column 10, lines 5-8) and anticipating the limitations of Claim 5. The reference also teaches humanized antibodies (column 18, lines 28-56), thereby anticipating the limitations of claim 6. The '220 patent teaches that a preferred embodiment is an agonist antibody that binds to the extracellular domain of the receptor (column 37, lines 26-27). One of ordinary skill would predict that an antibody that binds to the extracellular domain of the Mpl receptor is one that would bind to a "soluble Mpl", as the specification teaches that a soluble Mpl molecule is an Mpl lacking the entire or a portion of the transmembrane domain [paragraph 0190 of the instant application]. Thus, the limitations of claim 8 are anticipated. The reference teaches "affinity matured antibodies" and disclose preferred affinity matured antibodies will have nanomolar or even picomolar affinities (column 12, lines 10-13), thereby anticipating the limitations of claims 11 and 12. Therapeutic antibody compositions are also disclosed (column 38, line 36-39), thereby anticipating the limitations of claim 38.

Claims 42 and 43 are directed to an antibody comprising a heavy chain variable region containing a CDR1 amino acid sequence of SEQ ID NO:36 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, a CDR2 amino acid sequence of SEQ ID NO:37 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, and a CDR3 amino acid sequence of SEQ ID NO:38 in which one or more amino acid residues has been substituted, deleted, added and/or inserted which has the same activity of a second antibody whose heavy chain variable region comprises SEQ ID NOs 36, 37 and 38 and whose light chain variable region comprises SEQ ID NOs:93, 94, and 95. Claim 42 recites an antibody comprising a heavy chain variable regions which may comprise CDR regions which are totally different than the CDR regions of SEQ ID NOs:36-38. Given their broadest,

reasonable interpretation, the claims read on an antibody which exhibits the same characteristics of the generic antibody recited in Claim 32, that is, an antibody that recognizes the region of amino acids 26-274 of human Mpl. Therefore, the limitations of Claims 42 and 43 are anticipated by the agonist antibody taught by the '220 patent.

The reference is silent as to whether the disclosed antibody has a TPO agonistic activity of EC50 or 100 nM or lower (claim 13), 30 nM or lower (Claim 14) or 10 nM or lower. However, one of ordinary skill in the art would predict that an antibody that has all the other recited properties, including the claimed affinities would also have the claimed EC50's.

Since the Office does not have the facilities for examining and comparing applicant's antibody with the antibody of the prior art, the burden is on applicant to show a novel or nonobvious difference between the claimed product and the product of the prior art (i.e., that the antibody of the prior art does not possess the same material structural and functional characteristics of the claimed antibody). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.)-

Thus, the teachings of the '220 patent anticipates all the limitations of claims 1, 5-8, 11-15, 32, 33, 38, 42, and 43.

Claims 1-3, 5- 8, 11-15, 32, 33, 38, 42, and 43 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Tsuchiya et al (2004. US PGPUB 2004/0091475, published 13 May 2004, priority claimed to PCT/JP01/09259, filed 22 October 2001, cited on IDS of 23 May 2007, reference A11, the '475 reference)

The '475 reference teaches modified antibodies that recognize TPO receptors and exert TPO agonist activity [abstract and paragraph 0011]. The modified antibodies comprise H (heavy) chain V (variable region) and L (light) chain V region as a single chain polypeptide [paragraph 0013] thereby anticipating the limitations of claims 1, 32 and 33. The modified antibodies are single chain Fv polypeptides; these antibody fragments are encompassed by the term "minibody" [paragraph 0142 of the instant

specification]. Thus, the limitations of claim 7 are anticipated. The H chain V region and L chain V region are connected through a linker (chimeric antibody) in the modified antibodies [paragraph 0014], thereby anticipating the limitations of claims 3 and 5. The single chain modified antibodies comprise two or more H chain V regions and L chain V regions; a preferred arrangement comprises H chain V region-L chain V region-H chain V region-L chain V region [paragraphs 0053-0054]. The limitations of claim 2 are thus anticipated. The modified antibodies are humanized antibodies [paragraph 0033]; thus, the limitations of claim 6 are anticipated. The antibodies taught by the reference bind to a cell surface molecule (the extracellular domain) [paragraph 0009]. One of ordinary skill would predict that an antibody that binds to the cell surface TPO molecules would bind to a "soluble Mpl", as the specification teaches that a soluble Mpl molecule is an Mpl lacking the entire or a portion of the transmembrane domain [paragraph 0190 of the instant application]; thus, the limitations of claim 8 are anticipated. Pharmaceutical preparations containing TPO agonist modified antibodies are also taught [paragraph 0040], thereby anticipating the limitations of claim 38.

Claims 13-15 are directed to an antibody whose TPO agonistic activity is EC50=100 nM or lower, EC50=30 nM or lower, or EC50=10 nM or lower, respectively. The '475 reference teaches measurement of ED50. The ED50 is defined as a dose needed for achieving 50% reaction of the maximum activity set as 100% in the dose-reaction curve [paragraph 0018]. Absent evidence to the contrary, and in the absence of a clear definition of EC50 in the specification of the instant application, one of ordinary skill would interpret the ED50 as disclosed in the '475 reference to be identical to the EC50 recited in claims 13-15. Figures 58 and 59 of the '475 reference teach antibodies with ED50 values of less than 10 nM, thereby anticipating the limitations of claims 13-15

Claims 42 and 43 are directed to an antibody comprising a heavy chain variable region containing a CDR1 amino acid sequence of SEQ ID NO:36 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, a CDR2 amino acid sequence of SEQ ID NO:37 in which one or more amino acid residues has been substituted, deleted, added and/or inserted, and a CDR3 amino acid sequence of

SEQ ID NO:38 in which one or more amino acid residues has been substituted, deleted, added and/or inserted which has the same activity of a second antibody whose heavy chain variable region comprises SEQ ID NOs 36, 37 and 38 and whose light chain variable region comprises SEQ ID NOs:93, 94, and 95. Claim 42 recites an antibody comprising a heavy chain variable regions which may comprise CDR regions which are totally different than the CDR regions of SEQ ID NOs:36-38. Given their broadest, reasonable interpretation, the claims read on an antibody which exhibits the same characteristics of the generic antibody recited in Claim 32, that is, an antibody that recognizes the region of amino acids 26-274 of human Mpl. Therefore, the limitations of Claims 42 and 43 are anticipated by the agonist antibody taught by the '475 reference.

The reference is silent as the binding affinity of the antibody for soluble Mpl, as recited in claims 11 (An antibody whose binding activity to soluble Mpl is KD = 10^{-6}]k/l or lower) and 12 (An antibody whose binding activity to soluble Mpl is KD = 10^{-7} M or lower). However, one of ordinary skill in the art would predict that an antibody that has all the other recited properties, including the claimed EC50's would also have the claimed affinities for the Mpl receptor.

Since the Office does not have the facilities for examining and comparing applicant's antibody with the antibody of the prior art, the burden is on applicant to show a novel or nonobvious difference between the claimed product and the product of the prior art (i.e., that the antibody of the prior art does not possess the same material structural and functional characteristics of the claimed antibody). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.)

Thus, the teachings of the '475 reference anticipate all the limitations of claims 1-3, 5- 8, 13-15, 32, 33, 38, 42, and 43.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (2002. US 6,342,220, the '220 patent) as applied to Claim 1 above, in view of Hudson et al. (1999. J. Immunological Methods 231:177-189, cited on IDS of 23 May 2007, reference A67) The teachings of the '220 patent is outlined in detail above. The '220 patent does not teach an antibody wherein the two heavy chain variable regions and the two light chain variable regions are arranged in the order of heavy chain variable region, light chain variable region, heavy chain variable region, and light chain variable region from the N terminus of the single-chain polypeptide or an antibody wherein the two heavy chain variable regions and the two light chain variable regions are linked by linkers.

Hudson et al teach the making of high avidity scFv multimers (abstract). An example of an ScFv multimer taught by the reference is two ScFv monomers covalently fused by linkers comprising a V_H-Linker 1- V_L-Linker 2- V_H-Linker 3- V_L (Figure 2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '220 patent which teaches fragment agonist antibodies to Mpl including ScFv antibody fragments and construct scFv multimers comprising two ScFv monomers covalently fused by linkers comprising a V_H-Linker 1- V_L-Linker 2- V_H-Linker 3- V_L as taught by Hudson et al. The person of ordinary

skill in the art would have been motivated to make these modifications and would have anticipated success because Hudson et al teach that such constructs provide an increase in functional affinity for the appropriate antigen (page 178, 2nd column, 1st paragraph) and teach methods of constructing said antibody fragments.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuchiya et al (2004. US PGPUB 2004/0091475, the '475 reference). The teachings of the '475 reference are outlined in detail above. In addition to the teachings set forth above, the reference teaches the linkers connecting the variable regions of the modified antibody may be "have lengths of 1-30 amino acids, preferably 1-20 amino acids, more preferably 3-18 amino acids" [paragraph 0059]. The '475 reference does not teach an antibody wherein the linkers linking the variable regions comprise 15 amino acids.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '475 reference which teaches linkers of 3-18 amino acids and construct linkers of 15 amino acids. The person of ordinary skill in the art would have been motivated to make these modifications and would have anticipated success because:

In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) In re Geisler, 116 F.3d 1465, 1469-71, 43 USPQ2d 1362, 1365-66 (Fed. Cir. 1997) (MPEP 2144.05)

The claim recites a linker comprising 15 amino acids. This is within the narrow range of 3-18 amino acids taught in the '475 reference and is therefore obvious over the prior art.

Claims 16-18, and 23-28 are free of the prior art.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./
Examiner, Art Unit 1647

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647